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Research Paper

A flexible-dose dispenser for immediate and extended release 3D printed tablets

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ABSTRACT

The advances in personalised medicine increased the demand for a fast, accurate and reliable production method of tablets that can be digitally controlled by healthcare staff. A flexible dose tablet system is presented in this study that proved to be suitable for immediate and extended release tablets with a realistic drug loading and an easy-to-swallow tablet design. The method bridges the affordable and digitally controlled Fused Deposition Modelling (FDM) 3D printing with a standard pharmaceutical manufacturing process, Hot Melt Extrusion (HME). The reported method was compatible with three methacrylic polymers (Eudragit RL, RS and E) as well as a cellulose-based one (hydroxypropyl cellulose, HPC SSL). The use of a HME based pharmaceutical filament preserved the linear relationship between the mass and printed volume and was utilized to digitally control the dose via an input from computer software with dose accuracy in the range of 91–95%. Higher resolution printing quality doubled the printing time, but showed little effect on *in vitro* release pattern of theophylline and weight accuracy. Physical characterization studies indicated that the majority of the model drug (theophylline) in the 3D printed tablet exists as in a crystal form. Owing to the small size, ease of use and the highly adjustable nature of FDM 3D printers, the method holds promise for future individualised treatment.

1. Introduction

Personalised medicine provides patients with a superior treatment that takes into consideration their pharmacogenomics, anatomical and physiological particulars [1]. One major clinical aspect of personalised medicine is individualising the dose to suit an individual patient's need. In the United States, 30 million prescriptions are prepared annually by 3000 compounding pharmacies [2]. The most common dispensing problems facing these pharmacies were prescribing commercially unavailable drug combinations and strengths [3]. It is of significant importance to replace standardised dose tablet regimes with a dynamic-dose dispenser, which provides rapid and effective manufacturing for individual patient's needs.

For a tablet preparation method that meets the demands of personalised medicine, a safe and easily adjustable dispensing station must be created. The station should be operated via a simple user interface with minimal operation training required and can be connected to the wider healthcare network [4]. Clearly, such criteria cannot be fulfilled by conventional tableting methods, where multiple processing stages, large batches, use of costly facilities and experienced personnel are needed. This renders tailoring standard tabletting systems for personalised tablet manufacturing impractical when continuous modification to the doses is necessary.

The use of 3D printing as a flexible alternative method to conventional tableting techniques was first developed using powder-based 3D printing technologies [5–8]. Other printing techniques such as inkjet printing [9], thermal inkjet printing [10], piezoelectric inkjet printing system [11], selective laser sintering [12], stereolithography [13] and syringe/extrusion 3D printing [14] have also been investigated.

Fused Deposition Modelling (FDM) is a widely used and affordable bench top 3D printing technique. The potential of FDM-based 3D printers to incorporate drug molecules have already been investigated using commercially available PVA filaments [15–17]. Our research group showed the potential of this printing

Abbreviations: DSC, Differential Scanning Calorimetry; FDM, Fused Deposition Modelling; FFF, Fused filament fabrication; SEM, scanning electron microscopy; HME, Hot Melt Extrusion; HPC, hydroxypropyl cellulose; PVA, polyvinyl alcohol; TEC, triethyl citrate; TGA, Thermo Gravimetrical Analysis; USP, United States Pharmacopeia.

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technology to provide a mini-dispensing dose controlling station by manipulating the volume of the printed design through an order from computer software [4]. Nevertheless, previous attempts with FDM-based 3D printing displayed several limitations such as limited drug loading, the use of non-pharmaceutical grade ingredients, high temperature [4,16–18] and basic tablet designs. Pharmaceutical examples of FDM 3D printing were only confined to two polymers and extended drug release patterns [4,16,17,19,20].

In this study, a combined approach of manufacturing 3D printed tablet based on FDM 3D printing and Hot Melt Extrusion (HME) is presented. Theophylline was chosen as a thermo-stable model drug [21] and is commercially available as extended release formulation with dose range of 60–300 mg [22]. The potential of exploiting this approach to accurately control the dose of theophylline using a number of widely used immediate and extended release polymers in oral drug delivery was explored. The study was also carried out using a realistic drug loading (50%) with an easy-to-swallow caplet design.

2. Materials and methods

2.1. Materials

Theophylline was purchased from Arcos (UK). Eudragit RL100 and RS100 were donated by Evonik Industries (Darmstadt, Germany). Hydroxypropyl cellulose (SSL grade) was provided by Nisso Chemical Europe GmbH (Dusseldorf, Germany). Triethyl citrate (TEC) and triacetin were supplied by Sigma–Aldrich (UK). Scotch blue painter's tape 50 mm was supplied by 3 M (Bracknell, UK).

2.2. Preparation of theophylline loaded filaments via hot-melt extrusion

A MakerBot Replicator® 2X Experimental 3D Printer (MakerBot Industries, LLC, New York, USA) was utilized to print theophylline tablets. In order to fabricate drug-loaded filaments, a hot melt extrusion method was implemented using a Thermo Scientific HAAKE MiniCTW extruder (Karlsruhe, Germany).

The compositions of the mixtures of drug, polymer and plasticizer are detailed in Table 1. Approximately 6 g of each drug polymer and plasticizer blend was accurately weighed and added gradually to the counter flow twin-screw extruder. The molten mass was homogenised for at least 5 min to allow homogeneous distribution of the drug and the polymer(s). The specific temperature of initial feeding and extrusion for each filament are shown in Table 1. The extrusion was carried out through a die nozzle with cylindrical shape and a 1.5 mm diameter using a torque control of 0.6 N m. Filaments were stored in sealed plastic bags at room temperature before 3D printing.

2.3. Tablet design and printing process

Blank and theophylline loaded tablets were designed in caplet shape using Autodesk® 3ds Max® Design 2012 software version 14.0 (Autodesk, Inc., USA) and saved in STL format (Fig. 1C). The design was imported to the 3D printer's software, MakerWare Version 2.4.0.17 (Makerbot Industries, LLC., USA) (Fig. 1). A series of tablets with increasing volume was printed by modifying the dimensions of the design: Length × Width × Heights (L, W, H) without altering the ratios between these dimensions ($W = 0.364\ L$, $H = 0.396\ L$).

The volume of the rectangular prism that contains the tablet design (v) was calculated as:

$$v = LWH = L\ 0.364L\ 0.396L = 0.144144\ L^3 \quad (1)$$

In order to correlate the volume of the design and the mass of the printed tablet (M), a series of tablets of increased volume were printed and accurately weighed. A linear equation was established:

$$M = 0.7433\ V - 9.8967 \quad (2)$$

$$M = 0.10714\ L^3 - 9.8967 \quad (3)$$

Since the theoretical loading of the filament is 50% of its mass, the dose D (mg) is calculated as:

$$D = 0.5\ M \quad (4)$$

where M is the mass of the tablet. Therefore, the required dimension (L) to achieve a target dose (D) can be calculated as:

$$L = \sqrt[3]{\frac{2D + 9.8967}{0.10714}} \quad (5)$$

A series of tablets was printed according to Eq. (5) to achieve a target dose (D) of 60, 120, 200, 250 and 300 mg. Table 2 provided details of dimensions, expected and measured mass of these tablets.

2.4. Modification of 3D printer

A MakerBot Replicator® 2X Experimental 3D Printer (MakerBot Industries, New York, USA) was utilized to fabricate the caplet design. Tablets were printed using modified settings of the software for PLA filament as follows: type of printer: Replicator 2X; type of filament: PLA; resolution: standard; temperature of building plate: 20 °C; speed of extruder 90 mm/s while extruding and 150 mm/s while traveling; infill: 100%; height of the layer: 200 μm. No supports or rafts were utilized in the printed model.

The following modifications were implemented:

(i) Kapton tape layer (default) provided poor adhesion of the designs to the built plate. Blue Scotch painter's tape was applied to the surface of the printing board to improve adhesion to the surface layer.

Table 1
Processing parameters for filament production using HME and subsequent 3D printing.

Formulation (weight ratio)	HME process		3D Printing process	
	Initial temperature (°C)	Extruding temperature (°C)	Extruding temperature (°C)	Platform temperature (°C)
Eudragit RL/Theophylline/TEC 45/50/5	130	120	170	90
Eudragit RS/Theophylline/TEC 42.5/50/7.5	130	110	150	60
Eudragit E/Theophylline/TEC 46.5/50/3.5	130	110	140	60
Eudragit RL/Eudragit RS/Theophylline/TEC 22.5/22.5/50/5	130	120	150	90
HPC SSL/Theophylline/Triacetin 46/50/4	125	110	160	60

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